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# Chemometrics and the identification of counterfeit medicines—A review

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ABSTRACT

This review article provides readers with a number of actual case studies dealing with verifying the authenticity of selected medicines supported by different chemometric approaches. In particular, a general data processing workflow is discussed with the major emphasis on the most frequently selected instrumental techniques to characterize drug samples and the chemometric methods being used to explore and/or model the analytical data. However, further discussion is limited to a situation in which the collected data describes two groups of drug samples – authentic ones and counterfeits.

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## 1. Introduction

Counterfeit medicines pose a serious threat to public health [1]. In recent years a significant increase in the number of medicine counterfeiting cases has been observed. This can be explained by easier access to modern technologies that can be used to 'copy' authentic medicines on the one hand and a lack of effective control over the medicines that are introduced into a market by different illicit vendors via internet platforms on the other hand [2]. It is impossible to obtain precise estimates of the scale of drug counterfeiting. It can roughly be expected that ca. 10% of medicines enter the worldwide market as counterfeits. On a local scale, of course, the amount of detected counterfeit medicines may differ due to certain local factors (e.g. strict and less strict legal regulations). In highly developed countries, counterfeit medicines account for ca. 1% of the total controlled market. However, more than 50% of medicines purchased over the internet through sites that disguise their physical identity are fake or poor quality drugs. As discussed in reference [3], among the most common counterfeited medicines are antimicrobials (28%), hormones (22%), antihistamines (17%), vasodilators (7%), drugs for erectile dysfunction (5%) and anticonvulsants (2%). Bearing in mind the serious consequences and dangers related to counterfeit medicines as well as the steadily growing migration of medicines all over the world, new, relatively simple and effective methods that can support the detection of counterfeit medicines as well as certain strategies are strongly desired.

Authentic medicines can usually be distinguished from counterfeits by a careful analysis of their chemical composition [1]. The most important drug ingredients are the so-called active pharmaceutical ingredients (APIs). With respect to concentration of APIs, there are four groups of medicines: (i) medicines with the correct API content and appropriate dosage, (ii) medicines with the correct API content but inappropriate dosage, (iii) medicines with an incorrect API content and (iv) medicines without any APIs (placebos).

In many cases, identifying the authenticity of a drug based on the dose and type of APIs is insufficient. The presence of impurities may alter the expected pharmacological effect of a medicine and/or increase its toxicity considerably. In general, unexpected substances are present in samples as a result of poorly controlled manufacturing conditions, the use of low-quality substrates, APIs that are produced through a different process than the certified synthesis pathway, etc. The simplest approach to testing a drug's authenticity focuses on the assessment of a specific manufacturer tags, which are deliberately introduced in order to protect

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a product. These unique chemical or visual tags can be related to type/composition of the applied packing materials, unique holograms, labels imprinted on the surface of a tablet, etc. Another group of approaches relies on the characterization of the chemical composition of drugs. These concentrate on the analysis of the API content and, if necessary, a determination of a complete chemical profile. The API content that is found using a given analytical approach is then compared with the one declared by the manufacturer. Such a comparison is carried out by testing the null hypothesis postulating that there is no significant difference between the composition of the tested sample and the declared API level(s) using the *t*-test. Accepting the null hypothesis implies that a tested sample is authentic with respect to its API level. However, in most cases, determination of an API is insufficient to confirm authenticity. An alternative approach assumes that medicine samples are described by different unique instrumental signals without the need to determine the chemical content (the so-called chemical fingerprints) and/or additional parameters. Depending on the selected method, analytical data are collected with the hope that they can support the differentiation between authentic and counterfeit medicines. By definition such data are multivariate and thus their exploration and modeling requires the use of chemometric methods to extract useful chemical information.

In this review paper, we focus our attention on a presentation of the possibilities that arise from the effective use of chemometric methods in the field of drug verification, specifically those that are applied to distinguish between authentic and counterfeit drug samples. The list of chemometric approaches discussed in the consecutive chapters of this article is not exhaustive. However, it can be considered to be a good starting point for the further exploration of the chemometric toolbox. In supplementary material we provide a list of methods acronyms.

## 2. Analytical techniques used to describe medicine samples

Nowadays, various analytical methods are used to characterize medicines and verify their authenticity, see, e.g. [4]. In the toolbox of analytical methods one can find relatively simple ones such as the colorimetric methods, e.g. [5], dynamic thermal analysis [6] and advanced ones such as liquid chromatography (LC) [7], high-performance liquid chromatography (HPLC) [8], gas chromatography (GC) [9], capillary electrophoresis [10], mid-infrared spectroscopy and Raman spectroscopy [11], isotope ratio mass spectrometry (IRMS) [12], NMR spectrometry [13], mass spectrometry, etc. Hyphenated techniques are also often used. In general, these analytical platforms provide a user with large amounts of analytical data. A sample is usually characterized by hundreds or even thousands of measurements. This makes data exploration, modeling and interpretation very complex. Chemometric approaches can be used to deal with an excess of explanatory variables efficiently in order to extract meaningful information from the collected data. They are designed to study the possible relations and/or existing differences between different groups of samples (e.g. authentic and counterfeit medicines).

### 2.1. Chromatographic-based methods

Chromatographic techniques are most frequently used to determine the chemical composition of medicines [4]. The area of their application is very wide because they have the potential to separate the different components of mixtures and to deliver qualitative and quantitative information for them.

Simple thin-layer chromatography (TLC) has been effectively introduced in many laboratories whose focus is drug verification. Its popularity stems primarily from the low costs of an analysis, limited instrumental requirements and straightforward interpretation of separation results. Because of the simplicity of the TLC approach, one can find examples illustrating the use of TLC in the context of authenticity studies in the literature [14]. For instance, the detection of counterfeit Plavix® tablets can be achieved using the TLC separation of artemisinin and its derivatives followed by detection based on a color reaction [15].

High-performance liquid chromatography (HPLC) is probably the most popular instrumental chromatographic technique for the analysis of pharmaceuticals. It is regarded as a reference method in the qualitative and quantitative analysis of many pharmaceutical substances and also serves as a reference method in the validation of a large number of analytical techniques. HPLC systems can be equipped with various types of detectors that offer interesting detection properties, for instance, mass spectrometry (MS), diode-array detector (DAD) and evaporative light scattering (ELS), which help to increase the sensitivity, accuracy and precision of a method. These features are strongly desired especially when the analysis is focused on the chemical components that are present in a sample at low concentrations (e.g. impurities).

Gas chromatography (GC) is typically used for the analysis of volatile substances that are stable at high temperatures. Like HPLC, GC is accurate and repeatable and its sensitivity is determined by the detector that is (the type of mass spectrometer or flame ionization detection). In the context of drug verification, it can be used to determine the active substances, residual solvents and/or volatile impurities e.g. [9,16]. Since only a few medicines contain volatile components, the number of GC applications is smaller compared to the number of applications of HPLC or TLC.

### 2.2. Spectroscopic-based methods

Spectroscopic techniques operate at different ranges (energy) of electromagnetic radiation. Among the various methods, in the field of drug verification and analysis, applications of near infrared spectroscopy (NIR) [17], mid-IR analysis, FT-IR, FTIR-ATR, Raman spectroscopy [18] and nuclear magnetic resonance (NMR) [19] seem to dominate.

NIR is a spectroscopic technique that uses the near infrared region of electromagnetic radiation between ca. 700 nm and 2500 nm. It allows for the rapid analysis of samples without (or with very little) sample preparation. Spectra of the studied medicines can be obtained through packaging materials (glass or plastic blisters). Moreover, it is both non-destructive and cost-effective.

Raman spectroscopy is regarded as a versatile technique with respect to the form of a sample. It is used to analyze solid, liquid and gaseous samples. Moreover, it has the potential to perform measurements through coatings and packaging materials. Raman spectroscopy is highly selective, which allows molecules and chemical species that are structurally very similar to be identified and differentiated. Combined with chemometric methods, it has been applied in a wide range of studies focused on the identification of authentic drugs [20].

NMR spectroscopy is a frequently selected method for API verification [13], the identification of drug composition (including an analysis of impurities) [21] and for monitoring the production of medicines [22]. Moreover, the NMR spectra contain structural information that describes the sample components, which helps to determine their chemical structures. The sensitivity of this technique is insufficient for screening constituents at low concentrations as compared to the assessment of APIs (when peaks of active substances are well separated). The method is also applicable for the analysis of mixtures [19].

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